REMARKS

The present amendment is filed in response to the Office Action dated August 29, 2005. Claims 1-10, 14-26, 28, 31-44, 46-61 are now present in this case. Claims 1, 20, and 49-51 have been amended. New claims 56-61 have been added, and these claims find support throughout the application as filed, including for example page 6, lines 5-10 ("*the invention describes parsing of a population into selected phenotypic groups...*" including ARA and ARU; page 30, line 9 to page 32, line 28 (section beginning "*Individual Subject Analysis and Classification*" and continuing through the paragraph beginning, "*The patients are segregated into three phenotypic classifications...*").

The applicants wish to express their appreciation to the Examiner and the Examiner's supervisor for the personal interview with the applicants and the applicants' attorney on December 5, 2005. The technology developed by the applicants was discussed generally with the Examiner. In addition, the references of record in the case were discussed with the Examiner and distinctions between the cited references and the claimed invention discussed.

Applicants acknowledge receipt of the written Interview Summary in which the substance of the interview was indicated to be a discussion of the differences between the "super healthy" and the ARU population; identifying a drug target using candidate gene screening; and NIH risk analysis methods being a future predictive method. These issues are addressed herein, in the context of the issues raised in the Office Action.

Claims 1-10, 14-26, 28, 31-44, and 46-55 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The applicants respectfully traverse this rejection and request reconsideration. For ease of identifying the language in the specification, applicants refer the Examiner to Table 1 below, which summarizes the language noted by the Examiner and the relevant claim, and the corresponding support in the specification.

The goal of the written description requirement is to prevent applicants from claiming priority to earlier applications if the current application discloses new matter not present in the earlier applications (Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Further, In re Kaslow affirms that "the test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language" (707 F.2d 1366, 1375 (Fed. Cir. 1983)). The Examiner may have misapplied the written description requirement in this case. While the current application is a continuation of an earlier application as an RCE, the claimed subject matter is fully supported by the specification of the current application, and therefore the applicant does not need to demonstrate literal support in the specification for the claim language. Nevertheless, the support is present as discussed in the table and the subsequent text.

Table 1

Claim	Support in specification as filed
Claim 1, "using the data from the genetic differences between ARA and ARU subpopulations is not disclosed"	Page 4, lines 7-9: "...the genetic test results of the sub-population classified as *ARU* may be compared with the genetic test results of the sub-population classified as *ARA*." Page 5, lines 1-28, especially: Lines 16-18: "...a process by which specific populations of human subjects are ascertained and analyzed in order to discover naturally occurring genetic variations (or mutations) that confer resistance to disease." Lines 25-28: "...identification of a sub-population segment that has a natural resistance to a particular disease or biological condition further enables the identification of genes and proteins..."

Claim	Support in specification as filed
Claims 31-33: paragraph (c), Office Action page 4:	
Claim 31, "a drug target based on genetic differences"	Page 34, lines 8-13: "...the classification of patients into the *ARU* sub-population allows **genetic** analysis to focus on the reasons that a particular sub-population remains healthy in spite of being at significant risk for the biological condition of interest...the ideal **drug** is one that mimics the operation of protective mutations..."
Claim 32, "diagnostic assay based on genetic differences"	Page 34, lines 14-16: "Similarly, as one skilled in the art can appreciate, the knowledge gained from this **genetic analysis** can also form the basis for **diagnostic assay**..."
Claim 33, "vaccine based on genetic differences"	Page 34, lines 5-7: "Similarly, as one skilled in the art can appreciate, the knowledge gained from this **genetic analysis** can also form the basis for ...**vaccine development**."
Claim 41, system for data analysis to identify a target	Page 3, lines 12-13: "the analysis of medical histories comprises assigning numerical scores..." Page 5, lines 25-27: "identification of a sub-population segment that has a natural resistance to a particular disease of biological condition further enables the identification of genes and proteins that are attractive **targets for pharmaceutical intervention**..." Page 9, lines 27-29: "the invention provides a method for identifying and validating novel drug targets..." Page 13, lines 14-15: "Together, these **statistical analyses** directly indicate one or more putative **drug target genes**..." Page 14, line 21: "suitable **computing environment** in which the invention may be implemented..."
Claims 47-50, methods of identifying a "target," "diagnostics assay," "vaccine component," and "drug component" [Amended to recite "candidate drug" and "vaccine"]	Page 5, lines 25-27: "identification of a sub-population segment that has a natural resistance to a particular disease or biological condition further enables the identification of genes and proteins that are attractive **targets for pharmaceutical intervention, diagnostic evaluation, or prevention (e.g. prophylactic vaccination)**..." Page 9, lines 27-29: "the invention provides a method for identifying and validating novel **drug targets** and for enabling development of unique **diagnostic tests...**" Page 13, lines 14-15: "Together, these **statistical analyses** directly indicate one or more putative **drug target genes**..."

Claim	Support in specification as filed
Claims 50 and 51, "wherein identifying a target comprises identifying a drug component..." [Amended to recite "candidate drug"]	Page 5, lines 15-16: "a new genomics-based data processing strategy for the ready identification of highly validated **candidate drug** targets."
Claim 52, "configuration of a processor to identify a drug target based on genetic variations..."	Page 3, lines 16-17: "...may include **genetic** and/or biochemical testing." Page 5, lines 17-24, quoted in part: "...specific populations of human subjects are ascertained... to discover naturally occurring **genetic variations**...that confer **resistance** to disease..." Page 5, lines 25-27: "identification of a sub-population segment that has a **natural resistance** to a particular disease of biological condition further enables the identification of genes and proteins that are attractive **targets for pharmaceutical intervention**..." Page 14, line 21: "suitable **computing environment** in which the invention may be implemented..."
Claims 53-55, "identifying" drug component, diagnostic assay and vaccine, paragraph (h), page 6 [amended to recite "candidate drug"]	Page 5, lines 15-16: "a new genomics-based data processing strategy for the ready identification of highly validated **candidate drug** targets." Page 5, lines 25-27: "identification of a sub-population segment that has a natural resistance to a particular disease of biological condition further enables the identification of genes and proteins that are attractive **targets for pharmaceutical intervention, diagnostic evaluation, or prevention (e.g. prophylactic vaccination)**..." Page 14, line 21: "suitable **computing environment** in which the invention may be implemented..."

The discussion below corresponds to the paragraphs in the Office Action at pages 3-6.

(a) Claim 1. With respect to claim 1, the Office Action, on pages 3-4, cites language used to amend claim 1 in a previous amendment and states that "using the data from the genetic differences between ARA and ARU sub-populations to identify a drug target for a selected biological condition is not disclosed." (See Office

Action, page 4.) However, the specification, at page 4, lines 7-10, explicitly states that medical test results may comprise genetic test results and that *"genetic test results of the sub-population classified as ARU may be compared with the genetic test results of the sub-population classified as ARA."* This process is discussed in numerous sections of the specification as originally filed. For example, page 5, lines 1-18, discusses the overall approach to *"determine the genetic influences that allow people to remain healthy, even under conditions where they are expected to be sick."* (See page 5, lines 5-6.) The specification describes *"a new genomics-based data processing strategy for the ready identification of highly-validated candidate drug targets."* (See specification, page 5, lines 14-16.)

The specification further states that *"the identification of a sub-population segment that has a natural resistance to a particular disease or biological condition further enables the identification of genes and proteins that are attractive targets for pharmaceutical intervention, diagnostic evaluation, or prevention."* (See page 5, lines 25-28.) Thus, the specification clearly provides support for the process of identifying genetic variations between the ARA sub-population and the ARU sub-population. Those skilled in the art utilizing the present specification will readily realize the process for identifying drug targets associated with the selected biological condition based on those genetic variations.

(b) Claim 20. The Office Action states, at page 4, that the specification does not explain the use of a computer to identify drug target use in treating the selected biological condition. The specification describes a computer system at pages 14-17, but further describes the process of defining disease characteristics, risk characteristics and the classification of subjects into the ARA and ARU categories. The collection of medical, family, dietary, and behavioral histories are stored in the data structure 204. (See page 30, lines 6-8.)

Those skilled in the art will appreciate that computer systems are commonly used for the collection and analysis of such data. The individual subject analysis and classifications are described on pages 30-33. The use of the data stored in the computer data structure 204 is described in these passages. As noted above, those skilled in the art will appreciate that computers are commonly used for such

collection and analysis. The analysis details provided in the specification clearly describe how to utilize a computer system for the necessary analysis. The process of genetically analyzing study subjects is described in the specification. For example, at page 34, lines 5-17, the genetic analysis of study subjects, ARU patients, is described. Those skilled in the art utilizing the present specification will clearly understand the use of computers for genetic analysis of the ARA sub-population and the ARU sub-population.

(c) Claims 31-33. With respect to claims 31-33, the specification identifies targets as being drug targets, diagnostic assay targets, or vaccine targets based on genetic differences between the ARA and the ARU sub-populations. For example, the specification, at page 34, lines 9-17, discusses the classification of patients into a ARU sub-population to allow genetic analysis *"to focus on the reasons that a particular sub-population remains healthy in spite of being at significant risk for the biological condition of interest."* (See page 34, lines 10-13.) The specification further states that *"the ideal drug is one that mimics the operation of protective mutations that confer resistance to disease in the ARU sub-population."* (See specification, page 34, lines 14-15.)

That is, differences between the genetic test results of the ARA population and the genetic test results of the ARU population serve to identify protective changes, such as mutations, and may be used to readily identify a drug target, for example, to mimic operation of a protective mutation that confers resistance to disease in the ARU sub-population. As further noted in the specification, the genetic analysis may also form the basis for diagnostic assay or vaccine development. (See specification, page 34, lines 15-17.) That is, genetic differences between the ARA sub-population and the ARU sub-population are used to identify a target to be used in a diagnostic assay. Such an assay can be used, for example, to identify genetic predisposition to the selected biological condition.

This aspect of the claimed invention is addressed in the accompanying Affidavit under 37 C.F.R. § 1.132 of Shawn Iadonato, Ph.D. The Examiner's attention is directed to paragraphs 7 and 8 in which the genetic analysis of ARA and ARU populations matched for hepatitis C exposure and risk yielded a target, and the

corresponding drug is now in preclinical development. Thus, claim 31 is clearly supported by the written description in the specification. In the case of this target, the mutation rendered a protein beneficial in respect to its protection of an ARU individual. Mimicking this state is the desirable goal, so the mutated protein itself is the drug. In other situations, a loss of function might be desirable, in which case a vaccine against the target would be preferred. In both situations, the identification of the target automatically supports and describes a diagnostic assay, as detection of a mutation is known in the art using probes and other tools.

(d) Claim 41. With respect to claim 41, the Office Action states that the use of a processor to classify the subject populations in the identification of a target is not disclosed. The support in the specification for the use of computer implementation has been discussed above with respect to claim 20. For the sake of brevity, those arguments need not be repeated in their entirety. However, it is clear that the use of computers for the statistical and data analysis described herein is well-known. The use and value of computers in such analysis is readily understood, as is implementing the process described in the specification utilizing computers.

(e) Claims 47-50. With respect to claims 47-50, the Office Action states, at page 5, that the specification does not describe methods of identifying a target, diagnostic assay, vaccine component, and drug component based on test results from the ARA and ARU groups. This claim language is clearly supported in the specification at pages 32-34, and the specific term "candidate drug" has been used instead of "drug component," as indicated in Table 1 which cites to text support (e.g. page 5, lines 15-16). Section (11) at page 32 discloses the phenotypic classifications of ARA and ARU based on the test results of the steps performed in the previous sections (1) – (9), and section (14) at pages 33-34 discloses the identification of a mutation in the ARU group, *"a genetic mutation that confers a medical benefit that allows them to remain disease-free,"* wherein this protective mutation can be replicated by a pharmaceutical agent (i.e. a "drug"). Section (15) at page 34 reiterates the use of the ARU population's mutation or variant status for "drug discovery" and the use of this knowledge for diagnostic assay or vaccine development.

(f) Claims 50-51. With respect to claims 50-51, the Office Action states that the specification does not describe identifying a drug component (now "candidate drug," the term used in the specification) based on test results from the ARU and ARA groups. Section (14) at page 33 discloses the identification of a mutation in the ARU group, *"a genetic mutation that confers a medical benefit that allows them to remain disease-free,"* wherein this protective mutation can be replicated by a pharmaceutical agent (i.e. a "drug").

(g) Claims 52-55. With respect to claims 52-55, the Office Action states, on page 6, that the specification does not provide support for processor functions recited in the claims. The use of processors in genetic analysis is well-known. One skilled in the art applying the teachings contained within the specification as originally filed will clearly understand the application of processors to the task of analyzing genetic variations between ARA and ARU sub-groups.

In view of the foregoing discussion, applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement may be withdrawn.

Claims 1-10, 14-26, 28, 31-44, and 46-55 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Office Action, at pages 7-11, provides a detailed analysis of the drug discovery process and enumerates many alleged difficulties with traditional drug development processes. Such evidence does not render the present invention non-enabled for the precise reason that the invention is directed to a system of drug development that is not based on traditional drug development. In the discussion below, applicants review the grounds for the enablement rejection with reference to the accompanying Affidavit under 37 C.F.R. § 1.132 of Shawn Iadonato, Ph.D.

First, applicants respectfully submit that the claims are enabled under the standards set forth in Forman and Wands as cited by the Examiner.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re

Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q.2d at 1407. Thus, Wands supports the conclusion that in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma capable of making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole may yield negative results does not

mandate a finding that the amount of experimentation to achieve a positive result is undue.

Like the production of monoclonal antibodies, the identification of a drug target using methods of the present claims may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain a polypeptide that is within the scope of the claims. By following the guidance, applicants have developed such a target and a drug.

Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* The Wands court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (U.S.P.Q.2d at 1406.) The court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (U.S.P.Q.2d at 1406).

The present Office Action states that identification of a drug target "requires knowledge of the cause of disease and the biological systems associated with it." (See Office Action, page 7.) This is incorrect in relation to the claimed invention, and in fact the claimed invention bypasses this very requirement.

The background of the specification describes these precise difficulties associated with conventional drug discovery techniques. That is, the historical use of genomics in the drug development process is "a tool to understand disease and predict risks thereof." (See page 5, lines 1-3, emphasis added.)

In contrast, the disclosure describes a completely different paradigm in that *"rather than using genomics to understand why some people become sick, the present invention describes a process to determine the genetic influences that allow*

people to remain healthy, even under conditions where they are expected to be sick." (See page 5, lines 4-6.) The specification describes a process using *"genomics to identify mutations that lead to a healthy rather than a diseased phenotype"* thus providing *"a more efficient and directed process for identifying highly validated drug targets."* (See page 5, lines 1-3.) Thus, the present disclosure and accompanying claims are related to techniques for identifying individuals that have a desired healthy phenotype for a particular biological condition.

As one skilled in the art would appreciate, the study of the healthy phenotype does not require the detailed understanding of the knowledge of the cause of disease and biological systems associated with it, contrary to what is asserted in the Office Action. Thus, the undue experimentation referred to in the Office Action may be correct with respect to the old style of drug discovery by studying disease pathways, but is totally unrelated to applicants' pioneering method of discovering drug targets by studying those individuals that are phenotypically healthy in spite of high risk factors for a particular biological condition.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation. As disclosed in the accompanying Affidavit under 37 C.F.R. § 1.132 of Shawn Iadonato, Ph.D., these directions were followed for studying hepatitis C (HCV), which is disclosed in the specification at page 18, lines 17-20: *"populations that include individuals at high-risk for contracting HCV are identified (e.g., injecting drug users and hemophiliacs)."* From this analysis, populations of ARA and ARU individuals were in fact identified for HCV and differentiated on the basis of protective mutations in a single gene encoding the protein OAS1. This information led directly to the isolation of the mutated protein (the "target") and its use to inhibit viral growth in an *in vitro* model ("drug discovery"); preclinical experiments are ongoing.

In the Affidavit, Dr. Iadonato attests to the conclusion that when the guidance of the specification is followed, a target and drug are identified. It is important to note that this is the first such comparison that applicants undertook, and were successful the first time.

3. *Presence or absence of working examples.* As a working example, the specification provides a set of steps at pages 30-34. By following the methods disclosed in the specification, with reference to an exemplary disease disclosed in the specification (hepatitis C), applicants have identified a target related to HCV and a related drug, as discussed in detail in paragraph 2 above which is referenced herein as a working example.

4. *Nature of the invention.* The Office Action, at page 8, characterizes the nature of the invention by stating that computational tools "serve to produce a detailed picture of a protein family's involvement in a disease process and its potential as a drug target." This is irrelevant and also incorrect with respect to the pending application. As discussed in detail above, the claimed methods are directed not to the discovery of the disease process and proteins associated therewith, but to the *"identification of a sub-population segment that has a natural resistance to a particular disease or biological condition."* (See page 5, lines 25-26.)

Furthermore, the Office Action asserts that "bioinformatics methods have also been developed to virtually screen the target for compounds that bind and inhibit the protein in such a way as to not disrupt the normal metabolism." (See Office Action, page 8.) This is incorrect with respect to the present disclosure. As noted in the specification, *"therapeutic intervention would be presumed to show acceptable patient tolerance, as the desired outcome is to mimic the nature resistance phenotype of the healthy individuals."* (See page 6, lines 2-3.)

5. *The state of the prior art.* The state of the prior art is relevant to the extent that general methods of the invention are well-known, including identifying populations of patients, collecting patient samples, and performing polynucleotide sequencing and searching. These basic methods are known to one of skill and are applied in a new way as clearly taught by the specification. To the extent that "wet lab" experiments are performed, these can be concurrent with and/or subsequent to the inventive methods of genomic analysis and identification of the ARU and ARA groups for a particular disease state. Sample collection and sequence comparison are the key methods for identifying a target and a drug, not the experiments in physiology, biochemistry, molecular biology and genetics as listed in the Office Action. Although

such experiments could be concurrent with and/or after the target and drug have been identified, they are not required to practice the invention as claimed.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 U.S.P.Q.2d at 1406). By analogy, it would not defeat enablement for one of skill in the art to learn and become proficient in techniques for practicing the present invention.

The Office Action states, at page 9, that "the successful discovery of one drug target costs hundreds of millions of dollars and a period of research time that can span several years." This is incorrect with respect to the pending application. As noted by the inventors during the Examiner interview of December 5, 2005, the applicants have applied the teachings of the present disclosure to discover potential drug targets for use in the treatment of hepatitis C which is discussed in the specification (See, e.g., page 18, lines 22-25, page 25, lines 10-18, page 26, line 5 - page 27 line 13, page 28, lines 13-22 and page 29, line 18-page 30, line 8.) As noted in the Examiner interview on December 5, 2005, a drug target has been developed in much less time and at far lesser cost than alluded to in this factor.

Further details regarding development of a drug using the claimed methods, with attention to the amount of effort, is provided in the accompanying Affidavit under 37 C.F.R. § 1.132 of Shawn Iadonato, Ph.D. The affidavit directly addresses the Examiner's concerns about the cost and the research time. However, it must be noted that under Wands the amount of experimentation must not be "undue." The time invested may be extensive if routine screening is involved, which is the case for contemporary sequence analysis. Wands is also silent as to the cost, so the

Examiner's comment that discovery of a drug target could costs "hundreds of millions of dollars" is not dispositive of enablement under Wands.

7. *The predictability or unpredictability of the art.* The Examiner stated that drug target identification is a long process of trial and error requiring months to several years per drug target. This may be true for traditional drug discovery, which is one reason the applicants spent the time and effort to develop a new model of drug discovery that would not require the trial and error. As discussed in the Affidavit under 37 C.F.R. § 1.132 of Shawn Iadonato, Ph.D., a target corresponding to ARU group protection from hepatitis C infection was discovered on the first run of the claimed method, and the target translated directly into a drug based on the mutated protein. The Examiner should agree that this entailed less trial and error than the vast majority of drug discovery efforts, and furthermore since the drug is based on a chemical composition (a mutated protein) already found in healthy individuals (those at risk and unaffected by repeated exposure to HCV) it is predicted to have little or no toxicity, which is in marked contrast to the synthetic chemicals that are most often the result of traditional drug discovery. This eliminates much of the trial and error in terms of effective dose and toxicity.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the claimed methods would be more difficult and unreliable than known methods, and in fact as demonstrated by applicants for HCV, no difficulty or unreliability was encountered.

8. *The breadth of the claims.* At page 10, the Examiner states that "identifying and understanding the specific biological condition for which a drug will be developed is an additional complex process that adds to the complexity of drug target development." In fact, the beauty of the present invention is that it does not require an initial identification and understanding of the biological condition. Instead, it goes straight to nature for the answer, by studying a population (ARU) who should have a particular disease yet does not, and nature, through the genetic code, reveals what is different about these people when their genetic profile is compared to the matched ARA

group with the disease. This route of drug and target discovery is actually less complex than starting with a complex physiological pathway and determining by trial and error which aspect(s) of the pathway should be meddled with by which drug in order to obtain a phenotype that is the starting point of applicants' method.

The claims are not overbroad, because it is the method that is being claimed, not the applicability to some diseases and not others. In Wands the inventors randomly took a small subset of their frozen, stored hybridomas and tested them, finding that a certain percentage of the antibodies possessed the desired binding affinity. The Court noted that there was a discrepancy about whether the percent success should be measured against the antibodies tested or the total number left in the freezer and untested. The Court found that even if the success rate was very low, that would not defeat enablement if the experimentation was not undue:

> Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.
>
> (8 U.S.P.Q.2d at 1406, fn29)

Here, the first disease studied by the applicants confirmed that ARU and ARA populations could be identified for a complex virus, HCV, yet experimentation according to the invention yielded a target and a drug in a very short span of time. Based on Wands precedent this could be considered a 100% success rate.

At page 10, lines 8-9, the Examiner stated that "the results of experiments in genetic engineering are unpredictable." The relationship of that statement to the present claims is unclear, as the claims do not recite "genetic engineering." At page 11, lines 5-6, the Examiner stated that "the identification of a drug target requires the sorting out of 1000's of targets present in most organisms." Traditional drug discovery took this route. As pointed out above, the claimed methods rely in part on nature having done this "sorting out," and the sorting out is then identified by comparing the genetic background of the ARU population against the ARA population for a specific

disease to find out which gene nature has tinkered with to allow the ARU population to remain disease-free.

In the example of HCV, one gene was different in the ARU group (the intravenous drug users and the hemophiliacs who received contaminated blood products), not thousands. There is no reason to expect that other ARU groups will differ from the matched ARA group for a disease state by virtue of "thousands" of gene mutations, as this has never been the case in traditional drug discovery.

For the reasons discussed above, applicants respectfully request that the Examiner withdraw the rejection of claims 10, 14-26, 28, 31-44 and 46-65 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

Claims 1-10, 14-19, and 47-15 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite. The Office Action asserts that the phrase "ought to be affected" in claim 1 is indefinite because it lacks "clear and concise wording as to why members of the ARU sub-population ought to be affected." (See Office Action, page 11.) The applicants respectfully traverse this rejection and request reconsideration.

The applicants first note that the language of claim 1 presently objected to by the Examiner was suggested to the applicants by the previous Examiner as a means of distinguishing the ARU group members. Specifically, the phenotypic sub-population defined as "at risk and unaffected (ARU)" refers to members that should currently have a particular biological condition based on the assessment of risk factors associated with the biological condition. As defined in the specification, the ARU phenotypic group includes *"those apparently resistant individuals who have been exposed to significant risk but have failed to contract the disease."* (See page 6, lines 7-9).

Thus, the phrase in claim 1 where ARU members "ought to be affected" refers to individuals who ought to have the disease based on the assessment of risk factors, but for some reason do not have the disease. That is, they are at risk (i.e., ought to be affected), but are unaffected. In the context of a specific disease state, HCV, the at-risk unaffected (ARU) population is composed of intravenous drug users and hemophiliacs for whom exposure to HCV is documented, yet these people remain healthy. They should have the infection based on their exposure history and the

experience of their cohort ARA population who are infected. The applicants believe that the present wording clearly defines the ARU phenotypic sub-population. However, if the Examiner has suggestions for alternative language, the applicants are open to suggestion.

Claims 1-10, 14-26, 28, 31-44 and 46-55 stand rejected under 35 U.S.C. § 102(a) in light of a series of references directed to cancer screening methods established by NIH and collectively referred to as the NIH references. (See Office Action, page 12.) The applicants respectfully traverse this rejection and request reconsideration.

The cited references are as follows:

Reference A, "Susceptibility to Breast Cancer," Clinical Study started on February 8, 2000.

Reference B, "Genetic Testing for Breast Cancer Risk: It's Your Choice," August 14, 1997.

Reference C, "Risk Communication in Clinical Practice: Putting Cancer in Context," 1999.

Reference D, "Validation Studies for Models Predicting the Risk of Invasive and Total Breast Cancer Incidence," September 15, 1999.

Reference E, Archived version of the National Cancer Institute's Breast Cancer Risk Assessment Tool, June 20, 2000.

As noted in the Examiner interview on December 5, 2005, the NIH references are all used to predict the future possibility that an individual may contract breast cancer. The Gail Model in the NIH references is used to classify an individual "into a category with a specific risk of developing breast cancer in five years and lifetime." (See Office Action, page 13.) Thus, as the Examiner admits, the reference is an attempt to predict future risk of contracting breast cancer. As such, the NIH references bear no relation to the techniques recited in the claims. For example, claim 1 recites classifying the population into "at least two phenotypic sub-populations defined as at risk and affected (ARA), whose members have ever been affected by the selected biological condition, and at risk and unaffected (ARU), whose members ought

to be affected by the selected biological condition at the present time based on a risk analysis, but are unaffected by the selected biological condition at the present time." (Emphasis added) The two phenotypic sub-populations recited in claim 1 differ significantly from any population described in the NIH references by at least two different factors.

1. Claim 1 recites an ARA population whose members are affected by the selected biological condition. The entire concept of an ARA group is meaningless in context of the NIH references. The Gail Method, and the NIH references, talk about future risk. If an individual has breast cancer at the present time (i.e., they are affected) the NIH analysis is totally irrelevant. There is no need to predict future risk because the patient already has cancer. Thus, the concept of an ARA group is totally meaningless if applied to the NIH references. The NIH references do not teach or suggest an ARA phenotypic sub-population.

2. The concept of an ARU sub-population (should be affected but is not) is not taught or suggested by the NIH references. As noted in the Office Action, the NIH references are used to assess the future risk of contracting breast cancer, specifically, the odds of the individual patient developing breast cancer within five years and within the patient's lifetime. However, it is important to note that these are only predictions of future risk, and factors could come into play that would reduce or eliminate the risk, including hormonal changes, dietary changes, and exercise. In sharp contrast, the ARU phenotypic sub-population recited in claim 1 refers to members who should be affected by the selected biological condition at the present time. If the concept of claim 1 were extended to breast cancer, the ARU sub-population would include members who ought to have breast cancer at the present time based on risk analysis. The NIH studies refer to future risk, not present risk. For these reasons, among others, claim 1 is clearly allowable over the cited references. Claims 2-10, 14-19, and 47-50 are also allowable in view of the fact that they depend from claim 1, and further in view of the recitation in each of those claims.

Claim 20 is also a method claim. The ARA group recited in claim 20 refers to members of a subpopulation who are affected by the selected biological condition. As discussed above with respect to claim 1, the NIH references never

consider individuals who already have breast cancer. In the context of the NIH references, the term ARA is meaningless. For this reason alone, claim 20 is allowable over the cited references. Furthermore, claim 20 recites an ARU subpopulation "whose members remain unaffected by the selected biological condition and whose unaffected status is inconsistent with the risk status." The NIH references do not suggest such any subpopulation whose condition is inconsistent with the risk status. At best, some individuals in the NIH study are found to be at increased risk for developing breast cancer. However, nothing in the NIH references suggests any inconsistency between the affected status and the risk status. Accordingly, claim 20 is clearly allowable over the cited references. Claims 21- 26, 28, 31-40, and 51 are also allowable in view of the fact that they depend from claim 20, and further, in view of the recitation in each of the claims.

At page 14, lines 7-9 of the Office Action, the Examiner asserts that "all women" can be classified as members of a population that "ought to be affected by the selected biological condition at the present time based on risk analysis." This statement is made on the basis of a 10-13% risk of developing breast cancer in women generally (Office Action at page 14, lines 4-5). Applicants disagree with this interpretation. However, for the sake of argument, if all women ought to be affected by the biological condition (breast cancer), meaning they are "ARU," then there is no ARA group for comparison and the premise of the claimed method would not apply. None of the references suggest that all women ought to be affected by breast cancer at the present time. Instead, they seek to understand the complex multi-factorial causes of breast cancer so that women have an opportunity to modify their risk via diet, exercise, etc.

If fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258. A duplicate copy of this document is enclosed.

In view of the above amendments and remarks, the applicants respectfully request reconsideration and allowance of the application. If questions remain regarding the present application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
Charles L. Magness and Shawn P. Iadonato
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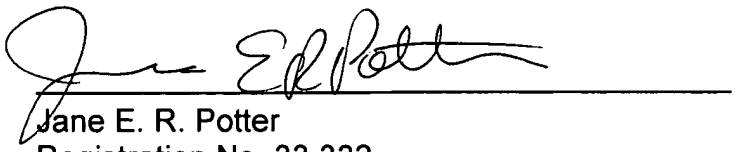

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